Gene Therapy: Successes, Challenges and Future Opportunities

Gene Therapy: Charting a Future Course

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What is Gene Therapy?

- Drug delivery platform, using non-viral or viral “vectors” to deliver genes to specific organs for the purposes of treating and/or preventing disease

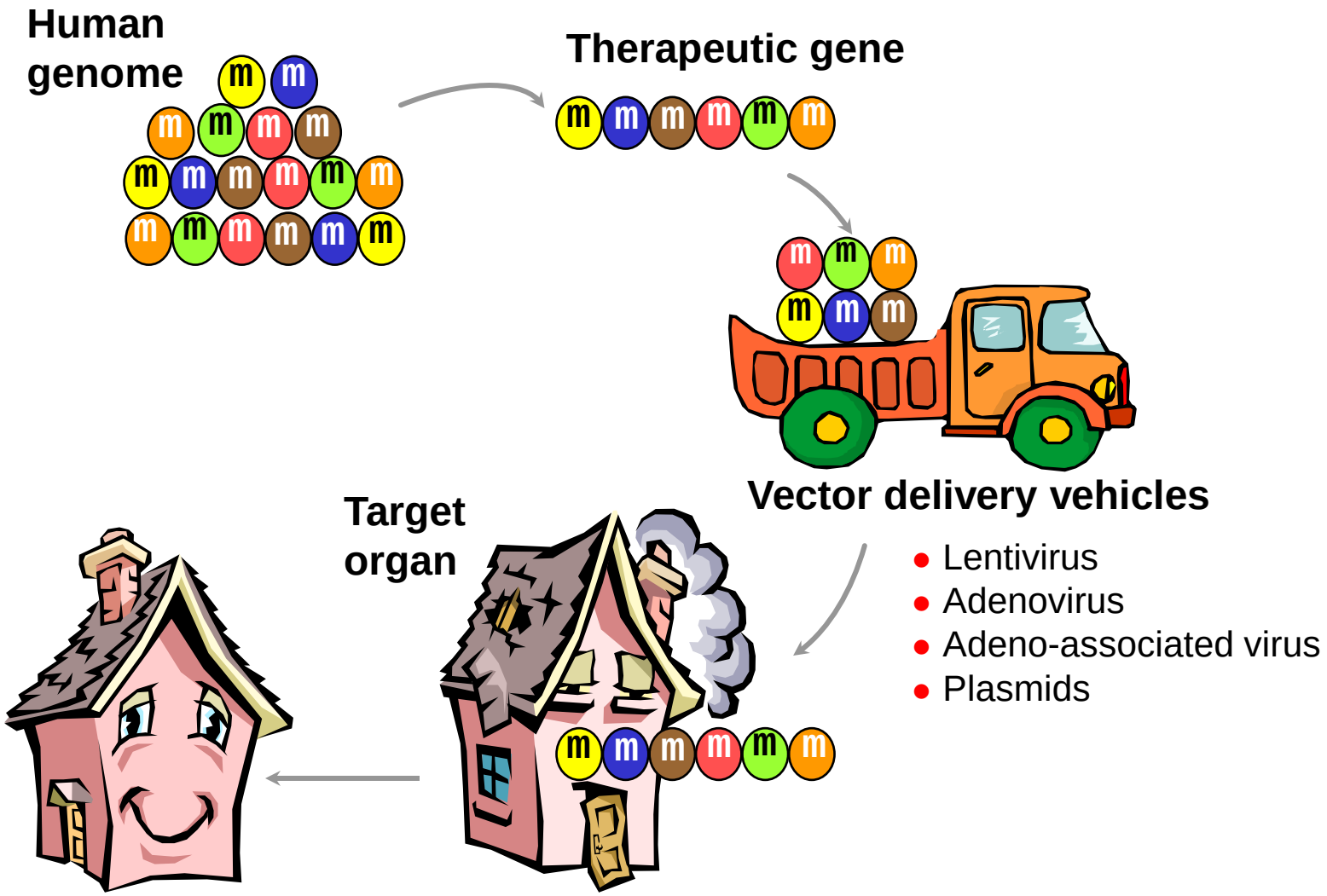
What Can Gene Therapy Do Better Than Other Drug Delivery Systems?

- Sustained delivery
- Steady state levels
- Local delivery
- Delivery of intracellular proteins
- Engineer cells to have novel functions for that cell type

Successes

- Vectors
- Clinical experience
  - Understanding the limitations and advantages of gene therapy
  - Application of the technology to successfully treat human disease

Successes – Vectors



Successes – Vectors

Well defined delivery vehicles

- Lentivirus – proliferating cells, integration
- Adenovirus – high levels, short term
- Adeno-associated virus – persistent expression, non-proliferating cells
- Plasmid/liposome – low level, short term

Successes - Lessons Learned from Clinical Gene Therapy Studies

- It is expensive to do clinical research
- For many applications, innate and adaptive immunity is our enemy
- Intravascular administration has dose limits
- Humans are much bigger than mice - scaling up from a mouse to a human is a challenge
- Different vectors → different pharmacokinetics
- It is easier to up-regulate than down-regulate
- Cannot genetically modify all cells in an organ
- Phenotype is critical

Successes – Human Diseases Can be Treated with Gene Therapy

- Lipoprotein lipase deficiency
- Inherited immunodeficiency
- Factor IX
- Retinitis pigmentosa
- Leukemia

What is the Most Important Lesson from the Clinical Successes?

- **All have a simply measured, clear phenotype**

Before

After

Lesson - All of the Human Diseases Successfully Treated with Gene Therapy Have a Simply Measured, Clear Phenotype

- Lipoprotein lipase deficiency
- Inherited immunodeficiency
- Factor IX
- Retinitis pigmentosa
- Leukemia

Challenges and Opportunities for the Future

- Establish standards
- Control of gene expression
- Genome, not cDNA, expression cassettes
- Specific genome insertion
- Join forces with stem/progenitor cell therapy
- Treatment of common, acquired disorders
- Double blind, placebo controlled trials
- Treatment of mild disorders
- Treatment of psychiatric and “social” disorders

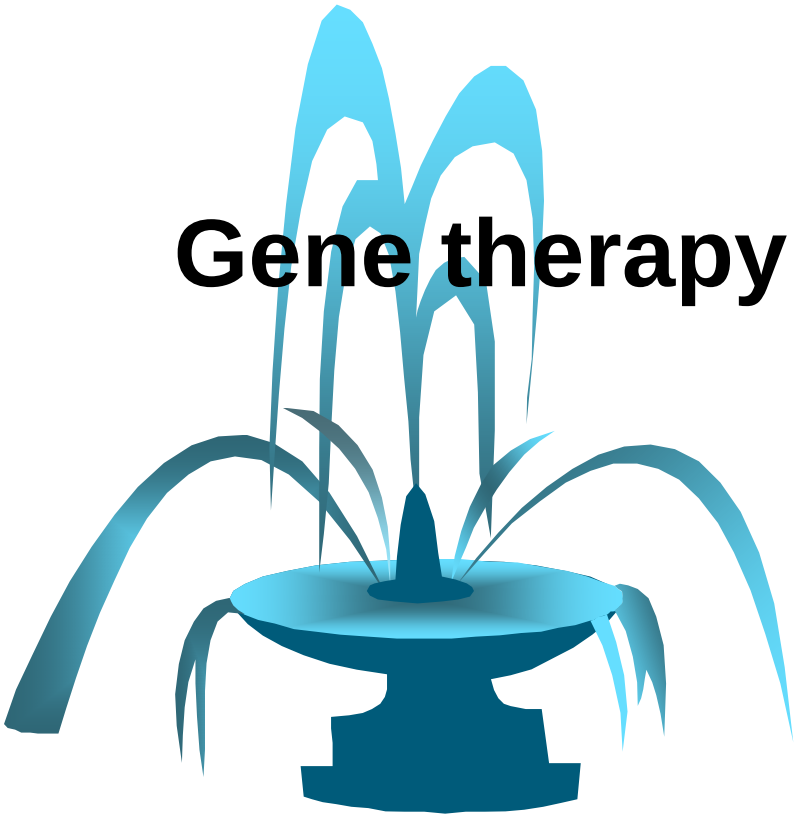
Guidelines for Future Success

- Choose the target carefully
- Keep it simple
- Recognize the financial limitations of academic (non-commercial) studies – this dictates the “n” and hence the choice of phenotype to be reversed
- Remember - humans are not mice

Future Opportunities

- Capitalize of the advantages of gene therapy as a drug delivery platform – local delivery, steady state levels, persistent expression, alter cell function

Gene Therapy in the 21st Century



Fountain of youth

Drug delivery platform